Complete Summary

GUIDELINE TITLE

Nonsurgical, aggressive therapy for non-small-cell lung cancer.

BIBLIOGRAPHIC SOURCE(S)

Gewanter RM, Komaki RU, Movsas B, Bradley J, Gopal RS, Lee HK, Rosenzweig KE, Thoms WW Jr, Kaiser LR, Schiller JH, Expert Panel on Radiation Oncology-Lung. Nonsurgical, aggressive therapy for non-small-cell lung cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 14 p. [32 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Komaki R, Sause WT, Byhardt RW, Curran WJ, Fuller D, Graham MV, Ko B, Weisenburger TH, Kaiser LR, Leibel SA, Choi NC. Non-small cell lung cancer, nonsurgical, aggressive therapy. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000 Jun;215(Suppl):1319-30.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Non-small-cell lung cancer

GUIDELINE CATEGORY

Treatment

CLINICAL SPECIALTY

Oncology
Pulmonary Medicine
Radiation Oncology
Radiology

INTENDED USERS

Health Plans
Hospitals
Managed Care Organizations
Physicians
Utilization Management

GUIDELINE OBJECTIVE(S)

To evaluate the appropriateness of treatment procedures for patients with non-small-cell lung cancer

TARGET POPULATION

Patients with non-small-cell lung cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Irradiation planning
2. Radiation therapy (RT) alone
3. Chemotherapy (chemo) alone
4. Combination therapy
    - Concurrent chemo/RT
    - Concurrent chemo/RT followed by chemo
    - Chemo followed by RT
    - Chemo followed by concurrent chemo/RT
    - Chemo followed by RT, followed by more chemo
    - RT followed by chemo
5. Surgery

MAJOR OUTCOMES CONSIDERED

- Progression-free, two-year, and five-year survival rate
- Median survival time
- Complications associated with treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer performed literature searches of peer-reviewed medical journals and the major applicable articles were identified and collected.

NUMBER OF SOURCE DOCUMENTS

The total number of source documents identified as the result of the literature search is not known.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Not Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

One or two topic leaders within a panel assume the responsibility of developing an evidence table for each clinical condition, based on analysis of the current literature. These tables serve as a basis for developing a narrative specific to each clinical condition.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Since data available from existing scientific studies are usually insufficient for meta-analysis, broad-based consensus techniques are needed for reaching agreement in the formulation of the appropriateness criteria. The American College of Radiology (ACR) Appropriateness Criteria panels use a modified Delphi technique to arrive at consensus. Serial surveys are conducted by distributing questionnaires to consolidate expert opinions within each panel. These questionnaires are distributed to the participants along with the evidence table

and narrative as developed by the topic leader(s). Questionnaires are completed by participants in their own professional setting without influence of the other members. Voting is conducted using a scoring system from 1-9, indicating the least to the most appropriate imaging examination or therapeutic procedure. The survey results are collected, tabulated in anonymous fashion, and redistributed after each round. A maximum of three rounds is conducted and opinions are unified to the highest degree possible. Eighty percent agreement is considered a consensus. This modified Delphi technique enables individual, unbiased expression, is economical, easy to understand, and relatively simple to conduct.

If consensus cannot be reached by the Delphi technique, the panel is convened and group consensus techniques are utilized. The strengths and weaknesses of each test or procedure are discussed and consensus reached whenever possible. If "No consensus" appears in the rating column, reasons for this decision are added to the comment sections.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

ACR Appropriateness Criteria®

Clinical Condition: Nonsurgical, Aggressive Therapy for Non-Small-Cell Lung Cancer

Variant 1: T1N3M0: 55-year-old patient with Stage IIIB (T1N3M0) poorly differentiated adenocarcinoma with a 2 cm nodule in RLL and a palpable supraclavicular lymph node. KPS >70, weight loss <5%.

Treatment	Appropriateness Rating	Comments

Treatment	Appropriateness Rating	Comments
Radiation therapy plus chemotherapy	8	
RT alone	2	
Chemotherapy alone	2	
Surgery	2	
Timing of Chemotherapy with RT—if given		
Concurrent chemo/RT	8	
Concurrent chemo/RT followed by chemo	8	
Chemo followed by concurrent chemo/RT	7	
Chemo followed by RT	2	
Chemo followed by RT, followed by more chemo	2	
RT followed by chemo	2	
Local Irradiation		
60-70 Gy/6-7 ½ weeks or biological equivalent	8	
55 Gy/7-8 weeks (split course)	2	
50 Gy/5 weeks	2	
45 Gy/3 weeks	2	
40 Gy/4 weeks	2	
30 Gy/2 weeks	2	
Radiotherapy Technique		
Multifield technique	8	
AP/PA only	2	
For Local Irradiation		
Computer planning	8	

Treatment	Appropriateness Rating	Comments
CT-based planning	8	
Complex blocking	8	
3D treatment planning	8	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: T2N3M0 (IIIB): 60-year-old male with NSCLC. Chest CT revealed a 5 cm mass in RML APW node enlargement. The patient has hoarseness due to paralyzed left vocal cord. KPS >70, weight loss <5%.

Treatment	Appropriateness Rating	Comments
Radiation therapy plus chemotherapy	8	
RT alone	2	
Chemotherapy alone	2	
Surgery	2	
Timing of Chemotherapy with RT—if given		
Concurrent chemo/RT	8	
Concurrent chemo/RT followed by chemo	8	
Chemo followed by concurrent chemo/RT	6	
Chemo followed by RT	6	
Chemo followed by RT, followed by more chemo	4	
RT followed by chemo	3	
Local Irradiation		
60-70 Gy/6-7 ½ weeks or biological	8	

Treatment	Appropriateness Rating	Comments
equivalent		
55 Gy/7-8 weeks (split course)	2	
50 Gy/5 weeks	2	
45 Gy/3 weeks	2	
40 Gy/4 weeks	2	
30 Gy/2 weeks	2	
Radiotherapy Technique		
Multifield technique	8	
AP/PA only	2	
For Local Irradiation		
Computer planning	8	
CT-based planning	8	
Complex blocking	8	
3D treatment planning	8	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: T3N3M0 (IIIB): 60-year-old patient NSCLC. Chest CT showed right paratracheal adenopathy with post obstructive pneumonia due to endobronchial lesion at the left mainstem. KPS >70, weight loss <5%.

Treatment	Appropriateness Rating	Comments
Radiation therapy plus chemotherapy	8	Concurrent chemotherapy should be started once pneumonia clears.
RT alone	2	
Chemotherapy alone	2	
Surgery	2	

Treatment	Appropriateness Rating	Comments
Timing of Chemotherapy with RT—if given		
Concurrent chemo/RT	8	
Concurrent chemo/RT followed by chemo	8	
Chemo followed by concurrent chemo/RT	2	
Chemo followed by RT	2	
Chemo followed by RT, followed by more chemo	2	
RT followed by chemo	2	
Local Irradiation		
60-70 Gy/6-7 ½ weeks or biological equivalent	8	
55 Gy/7-8 weeks (split course)	2	
50 Gy/5 weeks	2	
45 Gy/3 weeks	2	
40 Gy/4 weeks	2	
30 Gy/2 weeks	2	
Radiotherapy Technique		
Multifield technique	8	
AP/PA only	2	
For Local Irradiation		
Computer planning	8	
CT-based planning	8	
Complex blocking	8	
3D treatment planning	8	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9**		

Treatment	Appropriateness Rating	Comments
1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 4: T4N0M0 (IIIB): 60-year-old patient with left shoulder pain radiating in an ulnar distribution to the left upper extremity, accompanied by Horner syndrome. MRI of chest revealed a left superior sulcus tumor (SST) with limited involvement of the C7 and T1 vertebral bodies and left posterior 1st and 2nd ribs. Tumor was close to foramen between C7 and T1. FNA of left SST showed poorly differentiated adenocarcinoma. KPS >70, weight loss <5%.

Treatment	Appropriateness Rating	Comments
Radiation therapy plus chemotherapy	8	
RT alone	2	
Chemotherapy alone	2	
Surgery alone	2	Neoadjuvant chemoradiation may be considered in selective cases.
Timing of Chemotherapy with RT—if given		
Concurrent chemo/RT	8	
Concurrent chemo/RT followed by chemo	8	
Chemo followed by concurrent chemo/RT	2	
Chemo followed by RT	2	
Chemo followed by RT, followed by more chemo	2	
RT followed by chemo	2	
Local Irradiation		
60-70 Gy/6-7 ½ weeks or biological equivalent	8	

Treatment	Appropriateness Rating	Comments
55 Gy/7-8 weeks (split course)	2	
50 Gy/5 weeks	2	
45 Gy/3 weeks	2	
40 Gy/4 weeks	2	
30 Gy/2 weeks	2	
Radiotherapy Technique		
Multifield technique	8	
AP/PA only	2	
For Local Irradiation		
Computer planning	8	
CT-based planning	8	
Complex blocking	8	
3D treatment planning	8	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 5: T4N1M0: 60-year-old male with a few weeks history of superior vena caval obstruction (SVCO). Bronchoscopy revealed extrinsic compression of RUL. FNA showed undifferentiated large cell carcinoma. Chest CT showed 6 cm mass in RUL invading directly to mediastinum with compression of SVC and right hilar enlargement. KPS >70, weight loss <5%.

Treatment	Appropriateness Rating	Comments
Radiation therapy plus chemotherapy	8	
RT alone	2	
Chemotherapy alone	2	

Treatment	Appropriateness Rating	Comments
Surgery	2	
Timing of Chemotherapy with RT—if given		
Concurrent chemo/RT	8	
Concurrent chemo/RT followed by chemo	8	
Chemo followed by concurrent chemo/RT	2	
Chemo followed by RT	2	
Chemo followed by RT, followed by more chemo	2	
RT followed by chemo	2	
Local Irradiation		
60-70 Gy/6-7 ½ weeks or biological equivalent	8	
55 Gy/7-8 weeks (split course)	2	
50 Gy/5 weeks	2	
45 Gy/3 weeks	2	
40 Gy/4 weeks	2	
30 Gy/2 weeks	2	
Radiotherapy Technique		
Multifield technique	8	
AP/PA only	2	
For Local Irradiation		
Computer planning	8	
CT-based planning	8	
Complex blocking	8	
3D treatment planning	8	
Appropriateness Criteria Scale		

Treatment	Appropriateness Rating	Comments
1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 6: T4N2M0: 63-year-old male with hemoptysis and chest pain. Bronchoscopy revealed ulcerating carinal lesion. Biopsy showed SCC. Chest CT showed subcarinal lymph node enlargement. KPS >70, weight loss <5%.

Treatment	Appropriateness Rating	Comments
Radiation therapy plus chemotherapy	8	
RT alone	2	
Chemotherapy alone	2	
Surgery	2	
Timing of Chemotherapy with RT—if given		
Concurrent chemo/RT	8	
Concurrent chemo/RT followed by chemo	8	
Chemo followed by concurrent chemo/RT	2	
Chemo followed by RT	2	
Chemo followed by RT, followed by more chemo	2	
RT followed by chemo	2	
Local Irradiation		
60-70 Gy/6-7 ½ weeks or biological equivalent	8	
55 Gy/7-8 weeks (split course)	2	
50 Gy/5 weeks	2	

Treatment	Appropriateness Rating	Comments
45 Gy/3 weeks	2	
40 Gy/4 weeks	2	
30 Gy/2 weeks	2	
Radiotherapy Technique		
Multifield technique	8	
AP/PA only	2	
For Local Irradiation		
Computer planning	8	
CT-based planning	8	
Complex blocking	8	
3D treatment planning	8	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 7: T4N3M0: 58-year-old patient with a palpable right supraclavicular lymph node. Biopsy showed poorly differentiated NSCLC. Chest CT showed a small right pleural effusion which is too small to be tapped. KPS >70, weight loss <5%.

Treatment	Appropriateness Rating	Comments
Radiation therapy plus chemotherapy	8	
Chemotherapy alone	5	
RT alone	2	
Surgery	2	
Timing of Chemotherapy with RT—if given		
Concurrent chemo/RT	8	
Concurrent chemo/RT	8	

Treatment	Appropriateness Rating	Comments
followed by chemo		
Chemo followed by concurrent chemo/RT	8	
Chemo followed by RT	5	
Chemo followed by RT, followed by more chemo	5	
RT followed by chemo	2	
Local Irradiation		
60-70 Gy/6-7 ½ weeks or biological equivalent	8	
55 Gy/7-8 weeks (split course)	2	
50 Gy/5 weeks	2	
40 Gy/10 fractions split course	2	
30 Gy/10 fractions	2	
20-24 Gy/3-5 fractions	2	
Radiotherapy Technique		
Multifield technique	8	
AP/PA only	2	
For Local Irradiation		
Computer planning	8	
CT-based planning	8	
Complex blocking	8	
3D treatment planning	8	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 8: T1N0M0: 70-year-old male with long history of heavy smoking and COPD. Routine chest x-ray showed nodule of LLL. FNA showed NSCLC. (Medically inoperable). KPS >70, weight loss <5%.

Treatment	Appropriateness Rating	Comments
Radiation therapy plus chemotherapy	2	
RT alone	8	
Chemotherapy alone	2	
Surgery	1	
Timing of Chemotherapy with RT—if given		
Concurrent chemo/RT	2	
Concurrent chemo/RT followed by chemo	2	
Chemo followed by concurrent chemo/RT	2	
Chemo followed by RT	2	
Chemo followed by RT, followed by more chemo	2	
RT followed by chemo	3	
Local Irradiation		
60-70 Gy/6-7 ½ weeks or biological equivalent	8	
55 Gy/7-8 weeks (split course)	2	
50 Gy/5 weeks	2	
45 Gy/3 weeks	7	
40 Gy/4 weeks	2	
30 Gy/2 weeks	2	
Radiotherapy Technique		
Multifield technique	8	
AP/PA only	8	

Treatment	Appropriateness Rating	Comments
Stereotactic RT	6	
For Local Irradiation		
Computer planning	8	
CT-based planning	8	
Complex blocking	8	
3D treatment planning	8	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Summary of Literature Review

Stage I through stage IIIA non-small-cell lung cancer (NSCLC) patients can be operated on, with some advantage to receiving neoadjuvant or adjuvant chemotherapy with or without radiation therapy (RT). However, some patients with stage I through stage IIIA (surgically resectable) but having poor lung function or other medically inoperable conditions are candidates for aggressive RT with or without chemotherapy. These patients should be treated with 3-dimensional conformal radiation therapy (3DCRT) to minimize damage to surrounding normal tissue.

Stage IIIB includes patients with more extensive tumor invading the mediastinum (T4) and/or with metastasis to the contralateral mediastinum, contralateral hila, and ipsilateral or contralateral supraclavicular (N3). They are considered to be surgically unresectable and are usually treated by chemoradiation, RT alone, or chemotherapy alone depending on their performance status and their symptoms. Those patients who have better performance status and <5% weight loss need to be treated with a more aggressive approach, such as concurrent chemotherapy and RT. Some patients in this group, especially T4N0-1 patients, may become resectable after neoadjuvant therapy. Those patients who have pleural effusion are usually treated by chemotherapy followed by palliative RT when indicated to relieve symptoms. Patients with painful or obstructive lesions who are not otherwise candidates for definitive radiation may require prompt palliative RT rather than palliative chemotherapy alone.

Radiation Therapy Alone: Standard Fractionation

RT alone used to be considered the standard treatment for patients with unresectable and locally advanced NSCLC. RTOG® 73-01tried to optimize time/dose scheduling of RT alone for patients with unresectable and locally

advanced NSCLC, including those with poor performance status and >5% weight loss. This trial showed that better local control and 2-year survival were achieved by a total dose of 60 Gy in 6 weeks compared to a lower dose of RT alone. The investigators randomized 375 patients with inoperable or unresectable stage II and stage III cancer to be treated by 4 Gy/day x 5 days/week with a 2 week break and repeated 4 Gy/day x 5 days/week, giving a total dose of 40 Gy in 6 weeks (split course), 40 Gy in 4 weeks, 50 Gy in 5 weeks, or 60 Gy in 6 weeks with continuous RT (2 Gy/day without split). The overall progression-free survival rates were 46% among the patients who received 40 Gy with a split course, 51% for those who received 40 Gy continuous course, 65% for those who received 50 Gy, and 61% for those who received 60 Gy. The difference in the response rates was statistically significant (49% vs. 63%) between the groups who received 40 Gy and those who received 50–60 Gy. Two-year survival rates were 14% among the patients who received 40 Gy in 4 weeks with continuous course and 18% for those who received 50–60 Gy, compared to only 10% among those who received a split course, although this difference was not statistically significant. Patients who were treated with 50–60 Gy with clinical tumor control had a survival rate of 22% in 3 years compared to 10% if patients failed in the thorax. The initial response rate was significantly better among patients with adenocarcinoma and large cell carcinoma (69%) compared to those with squamous cell carcinoma (50%).

Altered Fractionation and Dose-Escalated Radiation Therapy

Because of the poor 2-year survival and local control with standard radiation doses and fractionation, a randomized dose escalation study was initiated through RTOG® 83-11. This trial was an attempt to increase local control by using higher total doses, while employing a twice-daily fractionation regimen to avoid increasing toxicities of late responding normal tissue. Eight hundred forty patients were treated with 1.2 Gy twice-daily fractionation separated by 4–6 hours. They were randomized to receive minimum total doses of 60 Gy, 64.8 Gy, and 69.6 Gy. After acceptable acute toxicities, 74.4 Gy and 79.2 Gy arms were added. The best arm received was 69.6 Gy in 6½ weeks and showed a 2-year survival rate of 29% for patients with good performance status and <5% weight loss, which was significantly better compared to the survival rates among patients who received lower doses.

The European Organisation for Research and Treatment of Cancer (EORTC) conducted a randomized study for patients with inoperable or unresectable stage II or III NSCLC who were treated by standard RT (60 Gy in 6 weeks) or continuous, accelerated, hyperfractionated RT (CHART). The majority of the patients had squamous cell carcinoma on histology. CHART was given at 1.5 Gy/fractions (Fx) 3 times a day, 7 days/week with at least 6 hours interfractional interval. The large volume dose was 37.5 Gy in 25 fractions followed by 16.5 Gy in 11 fractions, giving a total dose of 54 Gy. Their updated results showed improvement in survival and local control with CHART compared to standard RT (3-year survival rate with CHART was 20% vs. 13% with standard RT, and 3-year local control with CHART was 17% vs. 12% with standard RT). More moderate or severe acute dysphagia affected 49% of CHART cases, compared with 19% of those treated conventionally. However, there was no significant difference between the two arms in the rate of late complications.

Combined Chemotherapy and Radiation Therapy

Given the poor outcome with RT alone and the high rate of metastatic disease, combined chemotherapy and RT approaches were designed in an attempt to improve outcomes. The Cancer and Leukemia Group B (CALGB) randomized 155 patients with stage III NSCLC with good performance status and <5% weight loss who were treated with 2 cycles of vinblastine and cisplatin followed by RT (60 Gy in 6 weeks) or with RT alone (60 Gy in 6 weeks) Patients who were treated by induction chemotherapy followed by RT had a median survival of 13.8 months (78 patients) compared to 9.7 months for those (77 patients) treated by RT alone. The two-year survival rate was significantly better among the patients who receive combined treatment compared to those who received RT alone, 26% versus 13%. The longer follow-up of this study showed that the 5-year survival rate of patients who receive combined treatment was 19%, compared to 7% for those who received RT alone.

The RTOG® 88-08 randomized 452 patients with stage III NSCLC, good performance status, and <5% weight loss to be treated in three arms. Arm 1 received combined chemotherapy and radiotherapy (CRT). The chemotherapy, using vinblastine and cisplatin, was administered in 2 cycles and was followed by RT with 60 Gy over 6½ weeks. Patients in the other two arms received RT alone, one using 60 Gy of standard fractionation (ST) RT in 6 weeks, the other using 69.6 Gy of hyperfractionated (HFX) RT with a fraction size of 1.2 Gy. The median survival was 13.2 months in the CRT arm compared to 11.4 months among the patients who received ST RT. The two-year survival rate was 32% among the patients who received combined treatment vs. 19% among the patients who received ST RT alone. Outcome in the HFX RT arm was intermediate between the other 2 arms (median survival= 12 months; 2-year overall survival rate 24%). Five-year survival rates, however, were <10% in all the study arms.

Other phase III trials have been reported since 1988, including an EORTC study with a daily cisplatin and simultaneous RT arm, showing a significantly improved 2-year survival rate, 26% compared to 13% among the patients who received RT alone. However, the RT schedule was not considered optimal as a standard of RT in the U.S. The control arm of RT was given 3 Gy x 10 fractions with a 3- to 4-week break followed by 2.5 Gy x 10 Fx as a boost.

Other phase III trials have not found any significant improvement by adding chemotherapy to RT. One study reported that giving cisplatin concurrently with RT of 45 Gy in 3 weeks (3 Gy/day x 5 days/week) vs. RT alone (45 Gy in 3 weeks) did not show any significant difference in local control and survival. Another study randomized 121 patients to RT alone vs. cyclophosphamide, doxorubicin, and cisplatin as induction chemotherapy followed by RT. The latter did not provide any significant improvement in median survival.

Altered Fractionation Radiation Therapy Combined with Chemotherapy

The North Central Cancer Treatment Group (NCCTG) conducted a 3-arm Phase III randomized trial for patients with unresectable (stage III) NSCLC treated with standard fractionated thoracic RT, accelerated hyperfractionated thoracic RT, or HFX RT with concurrent etoposide and cisplatin. The standard fractionation was 60 Gy in 30 Fx over 6 weeks. HFX RT was given 1.5 Gy twice daily fractionation with

a 2-week break after initial 30 Gy in 2 weeks. This HFX RT was given alone or with concomitant cisplatin (30 mg/m^2, days 1-3 and 28-30) and etoposide (100 mg/m^2, days 1-3 and 28-30). The study group analyzed 99 eligible patients out of the 110 patients entered. There was a suggestion of improvement in the rate of freedom from local recurrence and survival for patients with HFX RT with or without chemotherapy, compared to standard RT. There was a significant improvement in survival with accelerated and HFX RT (with or without chemotherapy) in the subgroup of patients with non-squamous cell carcinoma. There was no difference in freedom from distant metastasis or survival among the patients who received HFX RT with or without concurrent chemotherapy. This study suggested that the patients with stage III NSCLC treated with accelerated HFX RT with or without chemotherapy may have better freedom from local progression and survival compared to those receiving standard RT, especially for patients with non-squamous-cell carcinoma.

The NCCTG next tested concurrent chemotherapy plus once-daily (qd) vs. twice-daily (bid) RT. Both arms received cisplatin (30 mg/m^2) and etoposide (100 mg/m^2) on days 1 and 28 concurrent with RT. Grade 3+ non-hematologic toxicity was slightly worse in the twice daily arm. At 2 years there was no difference in local control or overall survival. Subgroup analysis suggested a survival benefit to twice daily in non-squamous-cell histology, similar to previous findings by the NCCTG. This was in distinction to findings from RTOG® 94-10 (see below) that twice daily RT improved local control in squamous cancers.

RTOG® 91-06 combined the best arm of RTOG 83-11 (HFX RT to a total dose of 69.6 Gy) with concurrent oral VP-16 (50 mg twice daily for 14 days repeated every 29 days) and cisplatin (60 mg/m^2 on days 1 and 8 repeated every 29 days). The study showed a 2-year survival rate of 40% and median survival of 19.7 months among the patients with good performance status and <5% weight loss.

RTOG® 92-04 then compared the 91-06 regimen of immediate concurrent HFX RT and chemotherapy in a randomized phase II study with induction chemotherapy followed by concurrent chemotherapy and RT. Induction chemotherapy consisted of vinblastine (5 mg/m^2 intravenous bolus weekly, weeks 1-5) and cisplatin (100 mg/m^2 days 1 and 29 and 75 mg/m^2 on days 50, 71, and 92) with standard RT initiated on day 50, for a total tumor dose of 63 Gy in 34 fractions in 7 weeks. Arm 2 consisted of a total tumor dose of 69.6 Gy, 1.2 Gy/Fx twice-daily fractionation with 6 hours interfractional interval with cisplatin (50 mg/m^2 on days 1 and 2) and oral VP-16 (50 mg twice daily during the first 10 days of RT). The chemotherapy was repeated every 29 days x 2. One hundred sixty-eight patients were randomized and 160 were evaluable. There was no difference between the two arms in regard to overall survival. However, there was significant improvement in in-field progression at four years in arm 2 (30%) vs arm 1 (49%) at 4 years. There was significantly higher incidence of acute esophagitis among the patients who received concurrent chemotherapy and HFX RT. The latter regimen was included as one arm of the 3-arm phase III trial, RTOG® 94-10, described below.

RTOG® 98-01 was a randomized trial designed to test the hypothesis that the cytoprotectant amifostine (AM) would reduce the incidence of esophageal toxicity during concurrent chemotherapy and HFX RT. Patients received 2 cycles of induction chemotherapy with paclitaxel (225 mg/m^2) and carboplatin (area under

the curve [AUC] 6) on days 1 and 22, followed by concurrent weekly paclitaxel (50 mg/m^2) and carboplatin (AUC 2) with HFX RT (1.2 Gy bid to 69.6 Gy). Patients were randomized to receive or not to receive AM during the radiotherapy. The AM was administered once daily, 4 days a week, before the afternoon treatment. On RT-only days, AM was infused 15–30 minutes prior to RT administration. On days when chemotherapy was given, RT was to be administered not later than 180 minutes after AM administration. Acute esophagitis was graded using the NCI Common Toxicity Criteria (CTC), and patients kept a self-assessed swallowing diary. The results showed no significant difference in the incidence of CTC grade $\geq$ 3 esophagitis (30% with AM vs. 34% without AM); however, patient-reported swallowing symptoms were significantly less severe with AM, particularly in patients older than 65 years and in women. No differences in median survival or median time to progression were seen between the 2 arms. The authors concluded that while the trial did not support the hypothesis that AM reduces esophagitis, the findings of the patient-derived self-assessment suggested that further study of AM for non-squamous-cell lung cancer is warranted.

Sequential vs. Concurrent Chemotherapy and Radiation Therapy

The West Japan Lung Cancer Group conducted a Phase III study to investigate whether concurrent or sequential treatment with RT and chemotherapy improves survival for patients with unresectable stage III NSCLC. In the concurrent arm, chemotherapy consisted of cisplatin (80 mg/m^2 on days 1 and 29), vindesine (3 mg/m^2 on days 1, 8, 29, and 36), and mitomycin (8 mg/m^2 on days 1 and 29). RT began on day 2 at a dose of 28 Gy, 2 Gy/Fx, 5 Fx/week for a total of 14 fractions. This was repeated after a rest period of 10 days; the total tumor dose was therefore 56 Gy in 6 weeks. In the sequential arm, the same chemotherapy was given with RT initiated after completing 2 cycles of chemotherapy. RT consisted of 56 Gy, 2 Gy/Fx, and 5Fx/week with a total of 28 fractions. Three hundred twenty patients were entered in this study. The response rate for the concurrent arm was significantly higher (84%) compared to the sequential arm (66%). Median survival was significantly improved in patients receiving concurrent chemotherapy and RT (16.5 months) compared with those receiving sequential therapy (13.3 months). Two-, 3-, 4- and 5-year survival rates in the concurrent group were 34.6%, 22.3%, 16.9%, and 15.8%, respectively. The sequential group showed 27.4%, 14.7%, 10.1% and 8.9% in 2-, 3-, 4- and 5-year survival, respectively. Mild suppression was significantly greater among the patients who received concurrent chemotherapy and RT. There was no significant difference in regard to acute esophagitis between the two groups.

RTOG® 94-10 was a three-arm randomized trial comparing sequential (SEQ) chemotherapy followed by RT (once daily to 63 Gy), vs. two different concurrent chemoradiotherapy regimens. The latter consisted of either concurrent once-daily RT to 63 Gy (CON-QD), or concurrent twice-daily RT to 69.6 Gy (CON-BID). The SEQ and CON-QD arms each included 2 cycles of cisplatin and vinblastine. The CON-BID used 2 cycles of cisplatin and VP-16 based on the experience in RTOG® 92-04. Acute toxicity was worst in the CON-BID arm. Although time to in-field progression was best in the CON-BID arm, this did not translate into a survival benefit. The best survival was in the CON-QD arm, significantly better than the SEQ arm. Median survivals in the three arms were 14.6 months (SEQ), 17 months (CON-QD), and 15.2 months (CON-BID).

Role of Additional Chemotherapy before or after Concurrent Chemotherapy and Radiation Therapy

Several groups have studied the use of additional cycles of adjuvant chemotherapy in an attempt to improve outcomes. The CALGB recently presented initial results of trial 39801, in which patients with unresectable stage III disease were randomized to concurrent weekly carboplatin (AUC 2) and paclitaxel (50 mg/m^2) and 66 Gy once-daily RT, versus the same concurrent regimen preceded by 2 cycles of carboplatin (AUC 6) and paclitaxel (200 mg/m^2). A nonsignificant increase in median survival was seen in the induction arm (14 vs. 11.4 months), although the survival in both arms was poor compared with that seen in other recent studies. Significant toxicity was more common on the induction arm.

At the present time, combined treatment consisting of RT and chemotherapy has given better 5-year survival than RT alone for patients with medically inoperable and surgically unresectable stage III NSCLC. More recent results showed that concurrent chemotherapy and RT improved median survival and local control compared to sequential chemotherapy followed by RT. HFX RT and concurrent chemotherapy appears to give better local control, although survival has not been improved significantly compared to induction chemotherapy followed by concurrent low dose chemotherapy and daily RT. The risk of acute toxicity, especially esophagitis, is increased when HFX RT is combined with concurrent chemotherapy.

Chemoradiation Alone vs. Neoadjuvant Chemoradiation Followed by Surgery for pN2 Patients

Patients with stage IIIA disease, with metastatic involvement of ipsilateral mediastinal nodes (T1-3, N2) have traditionally been considered inoperable due to poor outcomes following surgical resection. Attempts have been made to improve the results of surgery in these patients with the addition of neoadjuvant chemotherapy with and without RT. Many consider chemoradiation alone to be the standard of care for these patients, particularly those with bulky nodal disease. The North American Intergroup 0139 (RTOG® 9309) trial was designed to compare definitive chemoradiotherapy with neoadjuvant chemoradiation followed by surgical resection. Patients in both arms received 2 cycles of cisplatin and etoposide concurrent with 45 Gy of RT. Patients without progression then went on to consolidation. Patients randomized to the surgery arm underwent attempted surgical resection, followed by 2 additional cycles of cisplatin/etoposide. Patients randomized to the chemoradiation arm completed RT to 61 Gy concurrent with 2 additional cycles of cisplatin/etoposide. Five-year progressive-free survival rate was significantly improved in the surgery arm (24.4% vs. 11.1%), but due to increased postoperative deaths, mainly following pneumonectomies, the overall survival benefit did not reach statistical significance (27.2% vs. 20.3% at 5 years). Patients downstaged to pN0 at surgery had a 5-year overall survival rate of 41%, compared to 24% in those with pN1-3. The results of this trial suggest that surgery after chemoradiation can be considered in fit patients, but that this approach may not be optimal in patients requiring a pneumonectomy.

Targeted Therapy

Given the overall poor results with standard cytotoxic therapies, and the number of advances that have been made recently in our understanding of the biology of cancer, a strong interest has emerged in targeting pathways unique to neoplastic cells or tumors. One such example is the epidermal growth factor receptor (EGFr), which can be inhibited by either monoclonal antibodies (e.g., cetuximab) or small molecule tyrosine kinase inhibitors (erlotinib or gefitinib). Another example is the area of angiogenesis, which can be inhibited with such drugs as bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF). Inhibition of both of these pathways (EGFr and VEGF) has been shown in randomized studies to prolong survival of patients with advanced NSCLC. However, in general little has been done with these drugs in earlier stage disease, although adjuvant studies are being planned with chemotherapy with or without erlotinib or bevacizumab. Other studies are being conducted with these agents when given with radiation therapy in inoperable stage III disease.

Neoadjuvant and adjuvant therapy are discussed more completely in the American College of Radiology (ACR) Appropriateness Criteria® topic: Induction and Adjuvant Therapy for N2 Non-Small-Cell Lung Cancer.

Abbreviations

- AP/PA, anterior-posterior/posterior-anterior
- APW, aortopulmonary window
- C, cervical
- COPD, chronic obstructive pulmonary disease
- CT, computed tomography
- 3D, 3-dimensional
- FNA, fine-needle aspiration
- KPS, Karnofsky Performance Status
- LLL, left lower lobe
- MRI, magnetic resonance imaging
- NSCLC, non-small-cell lung cancer
- RLL, right lower lobe
- RML, right middle lobe
- RT, radiation therapy
- RUL, right upper lobe
- SCC, squamous cell carcinoma
- SST, superior sulcus tumor
- SVC, superior vena cava
- SVCO, superior vena caval obstruction
- T, thoracic vertebra
- TNM, primary tumor, regional lymph node, and distant metastasis

CLINICAL ALGORITHM(S)

Algorithms were not developed from criteria guidelines.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based on analysis of the current literature and expert panel consensus.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Selection of appropriate treatment procedures for patients with non-small-cell lung cancer

POTENTIAL HARMS

- Complications associated with radiotherapy (e.g., acute dysphagia, acute esophagitis) and chemotherapy
- Morbidity and mortality associated with surgery

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

An American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those exams generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Gewanter RM, Komaki RU, Movsas B, Bradley J, Gopal RS, Lee HK, Rosenzweig KE, Thoms WW Jr, Kaiser LR, Schiller JH, Expert Panel on Radiation Oncology-Lung. Nonsurgical, aggressive therapy for non-small-cell lung cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 14 p. [32 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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1996 (revised 2006)

GUIDELINE DEVELOPER(S)

American College of Radiology - Medical Specialty Society

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GUIDELINE COMMITTEE

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology—Lung

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Richard M. Gewanter, MD; Ritsuko U. Komaki, MD; Benjamin Movsas, MD; Jeff Bradley, MD; Ramesh S. Gopal, MD; Hoon Ku Lee, MD; Kenneth E. Rosenzweig, MD; William W. Thoms, Jr, MD; Larry R. Kaiser, MD; Joan H. Schiller, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Komaki R, Sause WT, Byhardt RW, Curran WJ, Fuller D, Graham MV, Ko B, Weisenburger TH, Kaiser LR, Leibel SA, Choi NC. Non-small cell lung cancer, nonsurgical, aggressive therapy. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000 Jun;215(Suppl):1319-30.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

ACR Appropriateness Criteria® *Anytime*, *Anywhere*™ (PDA application). Available from the ACR Web site.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- ACR Appropriateness Criteria®. Background and development. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

PATIENT RESOURCES

None available

NGC STATUS

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